

The majority of the subjects who received VIT-45 completed the study. The incidence of premature discontinuations in the completed multicenter studies was 10% in the VIT-45 group which is comparable to that observed in the oral iron (9.6%) and Venofer (13.6%) groups. Reasons for premature discontinuation were generally comparable among the treatment groups, except that the incidence of adverse events leading to discontinuation were higher in the Venofer group (5.9%) compared to the VIT-45 (1.8%) and oral iron (2.1%) groups, demonstrating the overall tolerability of VIT-45.

The overall incidences of treatment-emergent adverse events were comparable between the VIT-45 (49.5%) and oral iron (51.2%) groups in the completed multicenter studies; the incidence in the Venofer group was lower (39.0%); however, the number of subjects in the VIT-45 group is almost 10-fold that of the Venofer group. Treatment-emergent adverse events experienced by $\geq 2\%$ of the 1095 VIT-45 subjects included headache (8.6%), abdominal pain (2.5%), nausea (2.4%), blood phosphate decreased (2.4%), hypertension (2.2%), nasopharyngitis (2.0%), and hypotension (2.0%). As expected, the most notable difference between subjects treated with VIT-45 and those treated with oral iron was for the incidence of gastrointestinal events (31.0% vs. 12.8%), specifically the incidences of constipation, diarrhea, nausea, and vomiting, which were more than double that observed in the VIT-45 group.

In the calculated dose/first-dose 1,000 mg studies, no statistically significant difference was observed between the VIT-45 (49.5%) and oral iron (51.2%) groups for the overall incidence of treatment-emergent adverse events. The incidence of gastrointestinal disorders was statistically significantly ($p < 0.0001$) higher in the oral iron group (31.0%) compared to the VIT-45 group (15.2%), while the incidences of adverse events associated with investigations and skin and subcutaneous tissue disorders were statistically significantly higher in the VIT-45 group (9.1% and 7.3%, respectively) compared to the oral iron group (3.9% and 2.4%, respectively). Among the gastrointestinal disorders, greater proportions of subjects in the oral iron group than the VIT-45 group experienced constipation, nausea, diarrhea, and vomiting, while a greater proportion of VIT-45 subjects experienced abdominal pain than oral iron subjects. Among the adverse events associated with investigations, greater proportions of VIT-45 subjects experienced blood phosphate decreased and GGT increased than oral iron subjects. Among the adverse events associated with skin and subcutaneous tissue disorders, greater proportions of VIT-45 subjects experienced rash and pruritus than oral iron subjects.

The only drug-related treatment-emergent adverse events reported by at least 2% of VIT-45 subjects in the calculated dose/first-dose 1,000 mg studies were headache (3.9%) and blood phosphate decreased (3.3%). The incidence of treatment-emergent adverse events reported on the first day of dosing in the calculated dose/first-dose 1,000 mg studies was statistically significant higher in the VIT-45 group compared to the oral iron group (6.8% vs. 2.7%). On the first day of dosing, the VIT-45 group had statistically significantly greater proportions of subjects who experienced general disorders and administration site conditions, primarily events associated with the site of study drug infusion, and skin and subcutaneous tissue disorders, primarily rash and urticaria, compared to the oral iron group.

The overall incidence of treatment-emergent adverse events was similar among VIT-45 subjects treated with either the 200 mg or 1000 mg doses. The only notable difference was for the higher incidence of headache in the 1000-mg group, which was almost double that observed for the 200-mg

group. No meaningful trends were apparent with respect to the incidence of treatment-emergent adverse events when analyzed by gender, age, race, weight, or etiology of anemia.

There were no deaths in the study attributed to VIT-45. The incidence of other serious adverse events among VIT-45 subjects was low (3% in all completed multicenter studies and 0.3% in the placebo-controlled, single-dose crossover study) and none were considered related to study drug. The incidence of premature discontinuation due to adverse events was comparable between the VIT-45 group (2.1%) and the other active treatment groups (3.1% oral iron and 2.5% Venofer). The incidence of drug-related treatment-emergent adverse events of hypersensitivity was 0.2%, the same as that observed with oral iron (0.2%). Drug-related mild or moderate hypotension was observed in 4 (0.2%) VIT-45 subjects, none of which were considered serious, led to premature discontinuation, or were symptomatic. Treatment-emergent adverse events indicative of potential allergic reactions including rash, pruritus, and urticaria were reported by $< 2\%$ of subjects who were treated with VIT-45; none of these events was considered serious and few led to premature discontinuation.

Laboratory evaluations of mean changes from baseline and potentially clinically significant values demonstrated no clinically meaningful changes for the majority of the parameters evaluated. However, during the conduct of the latter portion of the clinical program, transient, asymptomatic decreases in blood phosphate levels were observed among subjects treated with VIT-45. The decreases were apparent approximately 7 days after the initial dose of VIT-45 and the median time to recovery was approximately 2 weeks. No subjects reported an adverse event that was related to serum phosphate and no subject discontinued from the study due to decreased serum phosphate. The only predictor of change in serum phosphate was that subjects with higher baseline serum phosphate values had larger decreases in serum phosphate. The fact that the majority of oral iron-treated subjects also had a post-baseline decrease in phosphate and the negative correlation of baseline serum phosphate with changes in serum phosphate for both the VIT-45 and oral iron treatment groups suggest that the mechanism is intrinsic to iron therapy in this severely anemic population.

Overall, no clinically meaningful changes in vitals signs evaluations were associated with VIT-45 administration.

Safety data from more than 1700 subjects demonstrate the safety and tolerability of VIT-45.

What is claimed is:

1. A method of treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism resulting in reduced bioavailability of dietary iron, comprising administering to a subject in need thereof an iron carbohydrate complex in a single dosage unit of at least about 0.6 grams of elemental iron,

wherein,

the iron carbohydrate complex is selected from the group consisting of an iron mannitol complex, and an iron polyisomaltose complex, an iron polymaltose complex, an iron gluconate complex, and an iron sorbitol complex,

the iron carbohydrate complex has a substantially non-immunogenic carbohydrate component, and the disease, disorder or condition is not Restless Leg Syndrome.

2. The method of claim 1, wherein the iron carbohydrate complex has substantially no cross reactivity with anti-dextran antibodies.